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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,628	09/07/2005	Ignace Lasters	29248/28	4654

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
02/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,628	LASTERS ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,31,32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/01/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-15,31,32 are pending.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has not been filed in this National Stage Application.

Information Disclosure Statement

3. Applicants' Information Disclosure Statement filed 12/01/2004 has been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

Abstract

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-15,31,32 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

A. Claim 1, part b): the phrase "obtaining representations of peptide backbone structures of peptide located within the binding site of said MHC molecule" (emphasis added) is not clear. For a given peptide, representation of its structure does not depend on the presence of other molecules, e.g., an MHC molecule. How the peptide representations different if they are limited to being "located within the binding site of MHC molecule".

Please clarify via clearer claim language.

B. Claim 1, part c) : The phrase "modeling for each peptide... in relation to said MHC molecule". Modeling of what?

C. Claim 1, step d2): It is not clear what constitutes "conformational energy for the complete ensemble" – is it a sum, or average, or etc., of conformational energy of complex of the MHC molecule with each and every possible representation from step b)?

Further, which ensemble is meant? There are two occurrences of "ensemble" in the preceding part of the claim: ensemble of backbone structures (step b)), and ensemble of MHC/peptide complexes?

Claim Rejections - 35 U.S.C. § 101

The following is a quotation of the 35 U.S.C. § 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

6. Claims 1-15,31,32 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-15,31,32 are drawn to a computational method for predicting peptide's affinity. The claims do not recite any physical transformation step, nor they recite a tie to another category of invention.

To qualify as a statutory process, the claims should positively recite the other statutory class (the thing or product) to which it is tied, for example by identifying the apparatus that accomplishes the method steps, or positively recite the subject mater that is being transformed, for example by identifying the material that is being changed to a different state or thing. In the instant case, claims do not recite any physical transformation step. Further, there is no step in the claims that recites a tie to another category of invention. Therefore, the claims are drawn to non-statutory subject mater for failing to recite a step that ties the method to another category of invention.

A claimed process is patent-eligible under § 101 if it is tied to a particular machine or apparatus, or it transforms a particular article into a different state or thing. Thus, the machine-or-transformation test is a two-branched inquiry: an applicant may

show that a process claim satisfies § 101 either by showing that his claim is tied to a particular machine, or by showing that his claim transforms an article. See In re Bilski (Fed. Cir., October 30, 2008). The use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility. Further, the involvement of the machine or transformation in the claimed process must not merely be insignificant extra-solution activity.

Applicants' process is neither tied to a particular machine or apparatus, nor it transforms a particular article into a different state or thing. Thus, the claims fail the machine-or-transformation test and is not drawn to patent-eligible subject matter.

Note, that gathering data would not constitute a transformation of any article. A requirement simply that data inputs be gathered—without specifying how—is a meaningless limit on a claim to an algorithm because every algorithm inherently requires the gathering of data inputs.

Claim Rejections - 35 USC § 103.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-15,31,32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fothergill et al (WO 98/59244) in view of Background prior art

addressed in specification, as well as Rognan et al. (J.Med. Chem-42(22).4650-4658,1999) and Bohm et al. (Journal of Computer-Aided Molecular Design, Volume 8, Number 3, p. 243-256, 1994) and Miyazawa et al. (Proteins: Structure, Function, and Genetics, 1999, Volume 36, Issue 3, pages: 357-369), and Gohke et al. (Current Opinion in Structural Biology, Vol.11, Issue 2, 2001, p. 231-235).

The instant claims are drawn to method for predicting the binding affinity of a peptide for a major histocompatibility (MHC) class I or class II molecule, comprising the following steps:

a) receiving a representation of three-dimensional structure of an MHC class I or class II molecule,

b) obtaining an ensemble of representations of peptide backbone structures

c) modeling side chains for the backbone structures to obtain ensemble of MHC/peptide complexes, and

d) evaluating the binding properties of said peptide for said MHC molecule, by d1) evaluating potential energy, and d2) the conformational entropy for the ensemble.

Fothergill et al (WO 98/59244) is directed to method for the prediction of the binding affinity of a peptide to a MHC class II molecules comprising

a) receiving a representation of three-dimensional structure of an MHC molecule – see claim 1, for example.

b) obtaining an ensemble of representations of peptide backbone structures – see, e.g., paragraph bridging p. 8-9:

The conformation of the backbone of the peptide fragment is changed by modelling the conformation of the backbone on any one of 167 backbones which have been previously generated, based on human and murine crystallographic structures of MMC class II peptide complexes. The backbone conformation and the conformation of the peptide fragment side chains are altered systematically until the conformation score and the binding score of every possible conformation has been determined.

c) modeling side chains for the backbone structures to obtain ensemble of MHC/peptide complexes - see p. 5 and claim 1 and p. 5.

d) evaluating the binding properties of said peptide for said MHC molecule, by using two conformation scoring functions. See p. 5, for example:

The method of this invention thus involves assessing a binding score for all possible candidate peptides by considering the predicted three-dimensional conformations and interactions between the MMC and the peptide in the complex. The computed score indicates the predicted binding affinity for the particular peptide binding with the MMC allele and can be used to predict whether the peptides are likely to bind, or not.

Preferably, the conformation score for each pocket bound peptide side-chain is ascertained by considering at least one of the following parameters: a) the steric overlap between the pocket bound peptide residue bound in the pocket and an atom forming the pocket; this is value B, b) the number of hydrogen bonds which can be formed between the pocket bound peptide residue and an atom forming the pocket; this is value C, c) the strength of electrostatic interactions between any polar atoms of the pocket bound peptide residue and any polar atoms forming the pocket; this is value D, and d) the number of favourable contacts between the pocket bound peptide residue and the MMC residues forming one of the pockets; this is value E.

The reference does not address the scoring functions in terms used in the instant claims. However, it is conventional in the art of ligand/protein docking to use a plurality of scoring functions and their combinations to characterize binding affinity of a ligand. See, for example, vast amount of Background prior art methods addresses on pages 4-5,25-27 of the instant specification. A conformational scoring function usually evaluates potential energy of a complex wherein energy function may that include various components such as van der Waals interactions, H-bond formation, electrostatic interactions, etc.

Thus, Rognan et al. teach energy scoring function (FRESNO) to predict the binding free energy of peptides to class I major histocompatibility (MHC) proteins. The FRESNO function accounts both for the potential energy and entropy of a complex. See p. 4656, and discussion of the term ROT (right column), in particular.

Similarly, Bohm et al teaches scoring function that estimates the free energy of binding for a given protein-ligand complex of known 3D structure. The function takes into account hydrogen bonds, ionic interactions, the lipophilic protein-ligand contact surface and the number of rotatable bonds in the ligand. See Abstract. The Bohm function accounts for both potential energy and entropy of the complex. See see equation on p. 2 and description of term deltaGo on p. 245, second paragraph, p. 250, first full paragraph.

Similarly, Miyazawa et al. teach scoring function that estimates the free energy of binding for a given protein-ligand complex and evaluates stability of a specific conformation determined in relation to relative to the whole ensemble of protein conformations. See equation 7. Conformational state, E^{conf} is the conformational energy of state s of sequence i, and the sum is taken over all possible conformations. Therefore, the free energy of the whole ensemble can be regarded as a zero energy state, i.e., a reference state for an energy potential to represent protein stability (see explanation for equation 7). The estimate combines the free conformational energy and conformational entropy (σis a constant to represent the conformational entropy per residue for native-like structures – see explanation for equation 10).

Similarly, Gohlke et al reviews a variety of scoring functions used to evaluate protein–ligand binding. Majority of the energy functions combines energy and entropy terms – see discussion of "Regression-based scoring functions", and "First-principle-based approaches". The review concludes that the best strategy is combination of several scoring schemes into a consensus scoring approach. See Abstract and Conclusion.

In *KSR Int 'l v. Teleflex*, the Supreme Court, in rejecting the rigid application of the teaching, suggestion, and motivation test by the Federal Circuit, indicated that

> The principles underlying [earlier] cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.

KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007).

Applying the KSR standard of obviousness to it is concluded that the combination of scoring functions as instantly claimed is viewed as a combination of known elements, or as the simple substitution of one known scoring method for another, and that such combination or substitution would yield the predictable result of scoring the ligand-MHC binding, and is thus a "mere application of a known technique to a piece of prior art ready for improvement."

With respect to claims 10, 11, addressing evaluation of binding properties, when needed to evaluate stability of a protein/ligand complex a sum of the ensembles of

complexes is evaluated. See, for example Miyazawa et al. " the free energy of the whole ensemble can be regarded as a reference state for an energy potential to represent protein stability" (see explanation for equation 7). The estimate in Miyazawa et al combines the free conformational energy and conformational entropy ($\sigma$is a constant to represent the conformational entropy per residue for native-like structures – see explanation for equation 10).

With respect to claims 5-9, directed to modeling of side-chain conformations, there is a wide selection of known side-chain placement algorithms and evaluation of the resulting energy of a complex, such as DEE, CHARM, etc. See Background prior art methods addresses on pages 4-5,25-27 of the instant specification.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./
Primary Examiner, Art Unit 1631

mlb